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Pharmacokinetics of vinorelbine in patients with liver metastases

Background: The main elimination pathway of vinorelbine is hepatic metabolism, and the clearance of vinorelbine could be reduced in patients with liver metastases.

Objectives: To study the pharmacokinetics of vinorelbine in patients who have advanced breast cancer with or without liver metastases and to study the relationship between hepatic function and vinorelbine clearance.

Patients and Methods: We studied 29 patients with advanced breast cancer: 19 with liver metastases and 10 control patients with extrahepatic metastases (mean age, 61 years; age range, 38 to 81 years). The vinorelbine dose was 30 mg/m² as a short intravenous infusion; the dose was reduced by 50% in patients with bilirubin >2 mg/dl. Patients were classified by ultrasonographic estimation of the liver volume replaced by tumor (%LVRT). Standard liver function tests and a monoethylglycinexylidide test (a quantitative liver function test based on lidocaine metabolite formation) were performed. Vinorelbine was assayed in plasma by HPLC with fluorescence detection. Vinorelbine determination was impossible in two patients with more than 75% LVRT because of interferences. Pharmacokinetic parameters were calculated with a noncompartmental method and compared by means of the Kruskal-Wallis test.

Results: A lower vinorelbine clearance rate was observed in the five patients with more than 75% LVRT (22.9 L/hr/m²) compared with the 10 patients with no liver metastases (48.0 L/hr/m²) and the 12 patients with 25% to 75% LVRT (45.3 L/hr/m²). Terminal elimination half-life and apparent volume of distribution were not significantly different among groups. The monoethylglycinexylidide test had a significant correlation with vinorelbine clearance. ($r^2 = 0.70$; $p = 10^{-4}$).

Conclusions: These results support vinorelbine dose reduction in patients with severe liver failure but not in patients with moderate secondary liver involvement. The monoethylglycinexylidide test may prove to be useful for vinorelbine dose individualization. (CLIN PHARMACOL THER 1996;59:32-40.)

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The use of vinorelbine, a semisynthetic vinca alkaloid, is rapidly expanding for the treatment of malignant lymphoma, breast cancer, and lung cancer. This drug shows reduced neurotoxicity compared with other vinca alkaloids, and its dose-

limiting toxicity is neutropenia.^{1,2} Vinorelbine has a definite antitumor activity in breast cancer, and chemotherapeutic regimens that include vinorelbine are being developed for the treatment of advanced breast cancer.¹⁻³ Patients with liver metastases and various degrees of hepatic dysfunction could benefit from these treatments. Like the other vinca alkaloids, vinorelbine is eliminated through liver metabolism and biliary excretion.^{4,5} Package inserts and standard references recommend a dose reduction of vinorelbine in patients with liver failure to avoid severe toxicity.^{6,7} However, because data on vinorelbine pharmacokinetics in patients with hepatic dysfunction are lacking and because there is no unequivocal definition of liver failure, rational dosage guidelines are not yet available. To address these

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Table I. Individual CL rate and MEGX test results in patients receiving long-term therapy with CYP inhibitors or inducers

Patient No.	Group	Drugs	Potential effect on CYP	Vinorelbine CL		MEGX		Observed interaction
				L/hr/m ²	Percentile	µg/L	Percentile	
1	1	Amitriptyline, ranitidine	Inhibition	75	90	44.7	50	None
2	1	Lorazepam	Induction	41	25	48	50	None
3	1	Phenobarbital	Induction	48	50	105	90	Induction?
4	3	Amitriptyline	Inhibition	32	<10	30	25	Inhibition?
5	3	Lorazepam	Induction	43	50	60	50	None
6	3	Temazepam	Induction	41	50	58	50	None
7	4	Omeprazole, ranitidine	Inhibition	12	10	6	10	Inhibition?
8	4	Lorazepam, ranitidine	Induction, inhibition	22	75	40	90	Induction?

CL, Clearance; MEGX, monoethylglycinexylidide; CYP, cytochrome P450.

issues, we studied the pharmacokinetics of vinorelbine in patients who have breast cancer with liver metastases and in a group of patients with extrahepatic disease. Liver function was measured with a dynamic quantitative test on the basis of the formation of the major lidocaine metabolite, monoethylglycinexylidide (MEGX).^{8,9}

PATIENTS AND METHODS

Patients. We studied 29 patients with advanced breast cancer who were receiving single-agent vinorelbine therapy. Informed consent was obtained from the patients in accordance with institutional and international guidelines. All patients were female; mean age was 61 ± 11 years (age range, 38 to 81 years). They all had progressive disease after hormonotherapy; 16 patients had been pretreated with one, two, or three chemotherapeutic regimens (six, six, and four patients, respectively). Nineteen patients had liver metastases and 10 patients had extrahepatic metastases (skin, bone, lymphnodes, or lung). All subjects had normal creatinine levels (≤ 1.4 mg/dl).

No patients were excluded because of concurrent medications, and all long-term therapies were continued during the pharmacokinetic study. Patients who took drugs that have a possible interaction with vinorelbine or lidocaine metabolism are reported in Table I.

Liver assessment. Ultrasound and liver function tests were performed within 48 hours before the pharmacokinetic study. The patients underwent detailed ultrasound to determine the percentage of liver volume replaced by tumor (LVRT). This semi-quantitative estimation was based on the number of lesions, their diameter and morphologic pattern, and the number of hepatic segments involved. Ultrasound pictures were reviewed by an indepen-

dent observer to confirm the classification of each patient. The percentage of LVRT was classified in four groups, according to a common classification¹⁰⁻¹²: group 1 (0% LVRT); group 2 (1% to 25% LVRT); group 3 (26% to 75% LVRT); and group 4 (more than 75% LVRT). Standard liver function tests were performed: transaminases (AST and ALT), γ -glutamyltransferase (GGT), albumin, total bilirubin, and prothrombin time index (PT index). The MEGX test was performed as follows: after a blank blood sample, the patient received an intravenous dose of lidocaine (1 mg/kg) in 10 ml normal saline solution over 2 minutes. A blood sample was drawn 45 minutes after injection. The plasmatic MEGX concentration ($\mu\text{g/L}$) was measured by fluorescence polarization immunoassay (Abbott TDx, Abbott Diagnostic Ltd., Roma, Italy). In our laboratory, the sensibility of the test is 10 $\mu\text{g/L}$, and quality control samples that contain 50, 100, and 200 $\mu\text{g/L}$ have less than 10% interday variability (95% confidence interval).

Drug administration and blood sampling protocol.

The drug was given as a short (20 minutes) peripheral intravenous infusion in 250 ml normal saline solution, followed by a rapid flush of the vein with 100 ml normal saline solution. The standard dose (30 mg/m²) was empirically reduced by 50% in patients with bilirubin levels above 2 mg/dl (three patients from group 4 and one patient from group 3). Blood samples were drawn from the central line or from a contralateral venous site $\frac{1}{2}$, $\frac{3}{4}$, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours after the beginning of the infusion. Plasma was stored at -20°C until analyzed.

Vinorelbine pharmacokinetics was studied after the first dose. The drug was to be administered weekly (day 1, 8, and 21) until progression of disease or severe toxicity.

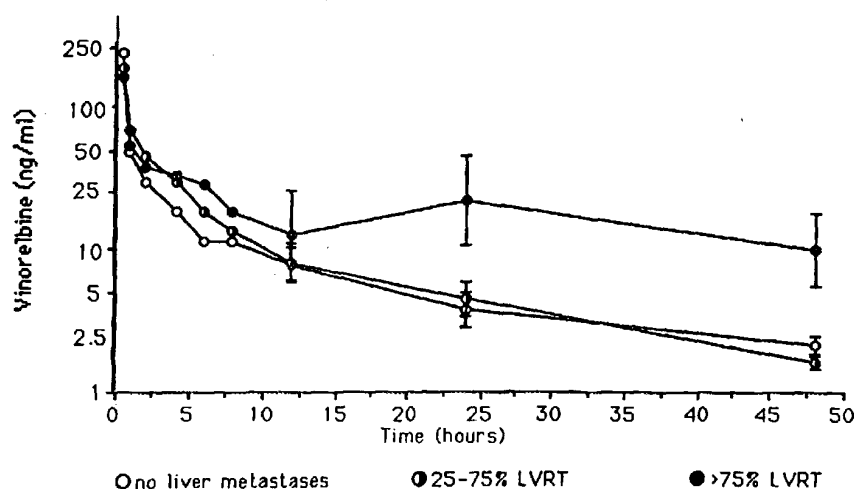


Fig. 1. Vinorelbine concentration versus time curve in the three study groups (mean and SE). % LVRT, Percent of liver volume replaced by tumor.

Measurement of vinorelbine plasma concentrations. Plasma concentrations were measured by an ion-pair reversed-phase HPLC method with fluorescence detection adapted from Debal et al.¹³ The method is described elsewhere in more detail.¹⁴ In brief, the chromatographic hardware included a Waters 510 pump, a Waters 717 autoinjector with a 200 μ l loop, and a Waters 470 fluorescence detector (Waters Chromatography, Milford, Mass.) linked to a Millennium 2000 chromatography manager software package. We used a 280 nm excitation and 360 nm emission wavelength for fluorescence detection. The mobile phase (a mixture of acetonitrile and 75 mmol/L phosphate buffer at pH 2.70 that contained 0.1 gm/L sodium dodecyl sulfate [60:40 vol/vol]) was eluted at 0.9 ml/min through a C_{18} chromatography column (3.9 \times 300 mm; Novapak, Waters Chromatography). Extraction from 2 ml plasma was performed in a two-step liquid-liquid extraction. After addition of 10 ng vinblastine (internal standard), a first extraction was done with 6 ml of ethyl-ether in glass polytetrafluoroethylene screw-cap tubes. After slow agitation for 45 minutes, centrifugation, and congelation, the supernatant organic phase was decanted into polyethylene tubes and evaporated to reduce either volume to 1 ml. A second, acidic extraction was then performed with 220 μ l of phosphate buffer at pH 2.7. After slow agitation for 45 minutes, 200 μ l of the acidic aqueous extract was injected into the HPLC system. Quantitation was

based on the internal standard method, using the ratio of peak areas of vinorelbine and vinblastine and two calibration curves for concentrations ranging between 2 and 25 ng/ml or between 25 and 1000 ng/ml. In the range from 2 to 1000 ng/ml, intraday variability is less than 7% and interday variability is 15%.

Pharmacokinetic analysis. The pharmacokinetic analysis was performed with use of a noncompartmental method.¹⁵ Area under the concentration-time curve from zero to infinity [$AUC(0-\infty)$] was measured with use of a trapezoidal rule and estimation of the log-linear terminal slope. Total body clearance (CL, in liters per hour per square meter) was calculated as a ratio of the vinorelbine dose (in milligram per square meter) and $AUC(0-\infty)$. Mean residence time (MRT, in hours) was calculated as the ratio of the area under the first moment curve and AUC. Apparent volume of distribution at steady state (V_{ss}) is the product of CL and MRT. C_{max} is the peak concentration observed; it was standardized by milligrams of vinorelbine dose (nanograms per milliliter per milligram). Terminal elimination half-life ($t_{1/2\gamma}$) was calculated from the slope of the log-linear terminal phase (after 12 hours).

Statistics. All analyses were done with use of non-parametric tests because several parameters did not follow a normal distribution (bilirubin, prothrombin time index, and AST). Pharmacokinetic parameters

Table II. Patient characteristics and vinorelbine pharmacokinetics in the study groups

	Group 1	Group 3	Group 4	p Value
LVRT	0%	25-75%	>75%	
n	10	12	5	
Age \pm SD (yr)	65 \pm 10	60 \pm 11	54 \pm 12	NS
Weight \pm SD (kg)	70 \pm 10	69 \pm 8	65 \pm 10	NS
C _{max} (ng/ml/mg)				
50th Percentile	3.6	2.3	3.0	NS
Range	1.7-8.9	0.8-11.1	1.3-6.3	
V _{ss} (L/m ²)				
50th Percentile	844	966	629	NS
Range	339-1819	170-1747	573-1187	
AUC(0- ∞) (μ g/L/hr)				
50th Percentile	626	630	968	0.06
Range	363-941	342-1072	624-1386	
CL (L/hr/m ²)				
50th Percentile	48.0	45.3	22.9*	0.005
Range	29.9-82.7	23.7-85.9	12.4-24.0	
MRT (hr)				
50th Percentile	18.8	19.2	28.6	0.10
Range	11.3-33.5	5.8-46.8	26.2-55.2	
t _{1/2γ} (hr)				
50th Percentile	26.2	24.3	25.7	NS
Range	21.1-33.3	15.7-38.5	24.8-40.8	

LVRT, Liver volume replaced by tumor; NS, not significant; C_{max}, peak concentration; V_{ss}, apparent steady-state volume of distribution; AUC(0- ∞), area under the concentration-time curve from zero to infinity; CL, total body clearance; MRT, mean residence time; t_{1/2 γ} , terminal elimination half-life.

*Significantly lower than group 1 and 3 with Kruskal-Wallis test.

and liver function tests were compared between groups with use of the Kruskal-Wallis test. The Spearman rank correlation coefficient was used to study the relationship between liver function tests and vinorelbine clearance. Least-square linear regression was used to calculate the equation that correlated clearance rate and MEGX test. These two continuous variables were normally distributed.

RESULTS

Ultrasonographic assessment of LVRT yielded the following groups: group 1 (0% LVRT), 10 patients; group 2 (1% to 24% LVRT), no patients; group 3 (25% to 75% LVRT), 12 patients; and group 4 (more than 75% LVRT), seven patients. All patients from group 4 had multiple confluent metastases in all liver segments. Group 2, which had no patients, was dropped from further analysis. In two patients with icterus and diffuse liver metastases (group 4), the chromatographic peak of vinorelbine was hidden by an unidentified high voltage peak eluting 1 minute earlier; this interfering peak was present in the pretreatment blank plasma sample and could not be separated from the vinorelbine.

Pharmacokinetic parameters are not available for these two patients.

The concentration versus time curve displayed a three-exponential decay. Fig. 1 shows the plasma concentrations (mean and SE) observed at each time point in the three groups. In all patients, vinorelbine was not detectable in the plasma after 72 hours. In patients from group 4 and in one patient from group 3, the plasma concentration decay was irregular and a second, lower peak was observed between 4 and 24 hours.

The pharmacokinetic results are summarized in Table II. Patients from groups 1 and 3 had similar pharmacokinetic parameters, and patients from group 4 had a markedly reduced clearance rate. A higher systemic exposure and a longer MRT were observed, although these differences were not statistically significant. C_{max} (standardized for dose), V_{ss}, and t_{1/2 γ} were similar in the three groups.

Table III shows the results of MEGX test and standard hepatic biochemistry. MEGX and albumin were lower and AST and bilirubin were higher in group 4 as compared with groups 1 and 3. GGT was higher in groups 3 and 4 compared with group 1.

Table III. MEGX test and standard hepatic biochemistry in the three study groups

	Group 1	Group 3	Group 4	p Value
LVRT	0%	25-75%	>75%	
n	10	12	5	
MEGX (μ g/L)				
Median	47	63	28*	0.005
Range	32-105	30-100	6.3-40	
PT index				
Median	1.00	0.99	1.11	0.07
Range	0.84-1.22	0.88-1.27	0.98-1.78	
Albumin (gm/dl)				
Median	4.15	4.30	3.80*	0.02
Range	4.0-4.5	3.6-4.9	3.5-4.2	
Bilirubin (mg/dl)				
Median	0.5	0.65	1.5*	0.004
Range	0.4-1.1	0.5-2	1.0-14.1	
AST (IU/L)				
Median	21	43	120*	0.004
Range	9-53	18-220	45-390	
GGT (IU/L)				
Median	27*	166	447	<0.001
Range	10-80	22-80	183-744	

PT, Prothrombin time; AST, aspartate aminotransferase; GGT, γ -glutamyltransferase.

*Significantly different from other groups with Kruskal-Wallis test.

Table IV. Correlation between hepatic function tests and vinorelbine clearance in the 17 patients with liver metastases

Hepatic function test	ρ	p Value
MEGX	+0.89	0.0005
PT index	-0.56	0.03
Albumin	+0.61	0.02
Bilirubin	-0.68	0.01
AST	-0.38	NS
GGT	-0.27	NS

 ρ , Spearman rank correlation coefficient.

Table IV shows the correlation coefficients between the various hepatic function tests and vinorelbine CL in patients with liver metastases (groups 3 and 4). A significant correlation was found between vinorelbine clearance and MEGX, bilirubin, albumin, and prothrombin time. The correlation between vinorelbine CL and MEGX test was remarkable, and is illustrated in Fig. 2. The individual CL rate and MEGX test are shown in Table I for the patients with potential drug-drug interactions.

DISCUSSION

Our objective was to study the pharmacokinetics of vinorelbine in patients with various degrees of

secondary liver involvement. Khayat et al.¹⁶ recently showed a direct relationship between plasma AUC and toxic neutropenia in patients treated with weekly vinorelbine. More information on pharmacodynamic relationships are required because other parameters, such as concentration of active metabolites, may also influence toxicity.¹⁷⁻¹⁸ Little is known about the pharmacodynamics of vinorelbine in patients with liver failure. Metabolite elimination may be slower in these patients, resulting in the accumulation of toxic metabolites. It should also be noted that vinorelbine has a very large volume of distribution, and plasma concentrations reflect a small part of the total amount of drug in the body. Modeling of vinorelbine concentrations in the effect compartment may be more appropriate.¹⁹ Without this knowledge, it is difficult to be confident about assertions for dosage reduction in this setting.²⁰ However, the results of Khayat et al.¹⁶ support that a higher systemic exposure results in a higher risk for severe hematologic toxicity, as is generally observed for vinca alkaloids and other antineoplastic drugs.²⁰⁻²³ Therefore in this study we assumed that dose individualization aims at achieving similar vinorelbine AUC values in all patients.

In Table V, data from our control group are compared with previously published vinorelbine pharmacokinetics. For the sake of comparison, our

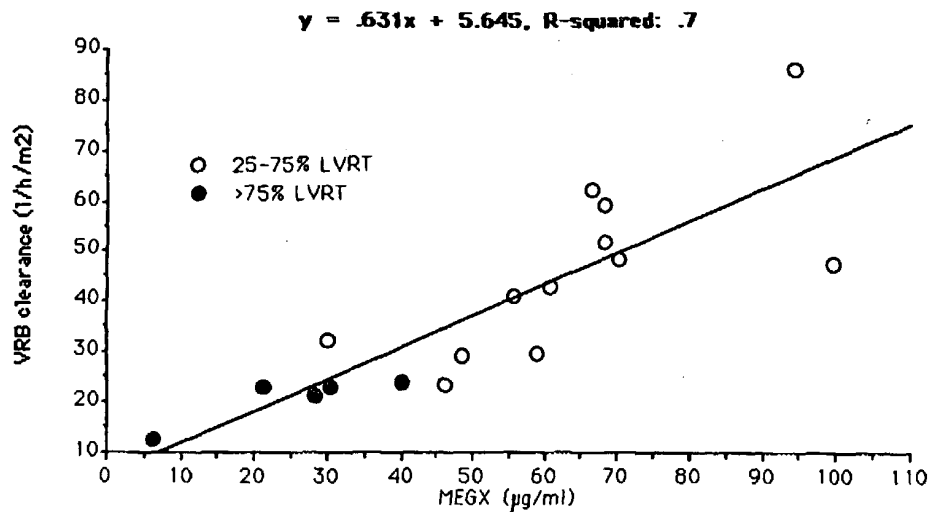


Fig. 2. Correlation between vinorelbine clearance and monoethylglycinexylidide (MEGX) test in patients with liver metastases ($n = 17$). % LVRT, Percent of liver volume replaced by tumor.

Table V. Pharmacokinetics of vinorelbine in patients without liver metastases (group 1): comparison with previously published data (mean)

	Group 1	Rowinsky et al. ²⁴	Marquet et al. ²⁵	Jehl et al. ¹⁷
No. of patients	10	16	8	20
Age range (yr)	46-81	43-62	51-74	41-74
Tumor type	BC	BC/NSCLC	NSCLC	NSCLC
CL (L/hr/kg)	1.24	1.21	1.28	1.26
V_{ss} (L/kg)	26	19	47.6	75.6
$t_{1/2\gamma}$ (hr)	26	18	44	42

BC, Breast cancer; NSCLC, non-small-cell lung cancer.

results are standardized here per weight (kilograms). Values for V_{ss} , CL, and MRT appear to be similar to those reported by Rowinsky in a group of 17 patients with solid tumors.²⁴ Vinorelbine terminal $t_{1/2}$ was slightly longer (26 hours) in our control patients than in patients in the above-mentioned study (19 hours). However, our data confirm that vinorelbine terminal $t_{1/2}$ is much shorter than was initially described: 44 and 42 hours in the studies of Marquet et al.²⁵ and Jehl et al.¹⁷ With a terminal elimination $t_{1/2}$ of about 1 day, no accumulation of the drug is expected with a 7-day dosing interval.

The profound reduction of vinorelbine CL in patients with diffuse liver metastases was expected because the parameters of hepatic function were se-

verely altered in these patients. Similar results had been observed for vincristine.^{5,23} Our data support the empirical vinorelbine dose reduction in patients with obvious signs of liver failure: hyperbilirubinemia, elevated transaminases, and prothrombin time in the context of numerous confluent liver metastases. In spite of a 50% dose reduction in patients with hyperbilirubinemia, a high systemic exposure was observed in most patients from group 4, putting them at high risk for toxicity. In these very compromised patients, the antitlastic treatment is given with a palliative intent, and caution should be exercised to avoid severe toxicity. It seems logical to reduce dosage by at least 50% in all patients with diffuse liver metastases, even if they have no major hyperbilirubinemia.

Dosage individualization in patients with moderate liver involvement is more controversial. In these patients, who are more likely to benefit from vinorelbine therapy, care should be taken to maintain an optimal dose intensity. Interestingly, our data indicate that in patients who have at least 25% of "normal" hepatic parenchyma, the mean vinorelbine CL is not reduced. Vinorelbine dosage should not be systematically reduced in these patients because it would result in a lower systemic exposure. However, an important variability of vinorelbine pharmacokinetics exists in patients with similar extent of liver metastases, suggesting that dosage guidelines should not be based only on ultrasonographic classification.

Standard hepatic function tests (albumin and prothrombin time) are of little help because they are altered only in preterminal patients. GGT is frequently altered in patients with moderate liver involvement, but we did not find any correlation with CL rate. In patient with bone metastases, alkaline phosphatases are elevated regardless of hepatic function. Tests for transaminase and bilirubin levels are the tests most commonly used by the clinicians, but these levels can be elevated in patients with obstructive or infectious disease who have no hepatocellular dysfunction.²⁶ In our patients, a weak correlation was observed between bilirubin and vinorelbine CL (Table IV). Because this correlation stems from 2 points with a very high bilirubin value, bilirubin would be a poor predictor of vinorelbine CL in patients with limited hepatic disease.

For vinorelbine dosage individualization, it seems relevant to use a dynamic quantitative assessment of liver function. Validated tests such as indocyanine green CL, antipyrine CL, and galactose elimination capacity are not readily feasible in bedside practice.^{9,26} In contrast, the MEGX test is rapid and relatively simple. It is a pharmacologic test based on the formation of the major lidocaine metabolite monoethylglycinexylidide (MEGX). Lidocaine undergoes an intense hepatic uptake and is metabolized to MEGX by the cytochrome P450 3A (CYP3A) (oxidative *N*-deethylation).²⁷ There is *in vitro* evidence that CYP3A also plays a major role in the biotransformation of vindesine, vinblastine, and probably all vinca alkaloids.⁴ MEGX formation depends mainly on hepatic blood flow and on intrinsic enzymatic activity.⁹ It is reduced and has a good prognostic value in liver damage of distinct mechanisms: acute anoxia (liver transplant donors),⁸ chronic alcohol exposure (cirrhosis),^{28,29} congenital

metabolic defects,³⁰ and viral infection (chronic hepatitis).³¹ We showed that MEGX formation is also reduced in patients with malignant hepatic infiltration from solid tumors.³¹ These were strong rationales for the use of the MEGX test as a predictor of vinorelbine clearance in this setting.

Our study documents a remarkable linear correlation between the MEGX test and vinorelbine CL ($r^2 = 0.70$). Seventy percent of the variability in vinorelbine CL can be "explained" by this liver function test in patients with liver metastases (Fig. 2). These data suggest that the MEGX test might be useful in the prediction of the individual vinorelbine CL rate. The potential role of the MEGX test for vinorelbine dose individualization should be prospectively studied. It may also prove to be useful in predicting pharmacokinetics for drugs that are metabolized by CYP3A (e.g., other vinca alkaloids, paclitaxel, and cyclosporine).

Most of our patients were receiving long-term oral therapy for various symptoms or comorbidity. It was not feasible to interrupt these treatments during the time of the pharmacokinetic study. Moreover, abrupt changes in the therapy would have caused unstable pharmacologic conditions. We attempted to identify possible drug-drug interactions and to determine whether these interactions might have influenced our main results (Table I). Except for one patient taking phenobarbital, no patients were taking any drug frequently involved in metabolic interaction (e.g., cimetidine, amiodarone, valproate, or phenytoin). In the patient taking phenobarbital (patient 3), we observed a very high MEGX value, most probably attributable to enzymatic induction by the barbiturate.³² However, vinorelbine CL was not increased. One patient from group 3 (patient 7) had received long-term treatment with ranitidine and omeprazole: both drugs are weak inhibitors of cytochrome P450.³³⁻³⁴ Although we cannot rule out a metabolic inhibition, the low vinorelbine CL and MEGX value are fully explained by the severe liver failure (PT index, 1.78; bilirubin, 14 mg/dl; AST, 390 UI). In the other patients taking ranitidine (patients 1 and 8), we did not observe an inhibition of lidocaine or vinorelbine metabolism. Metabolic inhibition by amitriptyline may explain the low vinorelbine CL and low MEGX observed in patient 4 in spite of a normal hepatic function (PT index, 0.88; AST, 25 UI; bilirubin, 0.7 mg/dl).³⁵ These drug interactions may account for some of the variability of vinorelbine pharmacokinetics; however, they do not alter our main results.

In conclusion, our data show that vinorelbine CL is reduced in patients with massive liver metastases from breast cancer. These results confirm the need for lower vinorelbine doses in these patients. Conversely, vinorelbine CL is normal in patients with moderate liver involvement. They should not be systematically treated with reduced doses because it would lower systemic exposure and might negatively affect antitumor activity. Vinorelbine dose individualization seems to be prudent in patients with liver dysfunction. It could be based on a quantitative liver function test such as the MEGX test.

We thank Research Nurse Anna Maria Colussi for her help in this study.

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